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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/632,281	08/01/2003	William Leon Elliott	PC20553A	5098

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EXAMINER	
DELACROIX MUIRHE, CYBILLE	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 02/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/632,281	ELLIOTT ET AL.	
	Examiner	Art Unit	
	Cybille Delacroix-Muirheid	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6-10 and 12-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-10 and 12-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *06/20/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

The following is responsive to applicant's amendment received Nov. 8, 2005.

Claims 3, 5, 11 are cancelled. No new claims are added. Claims 1-2, 4, 6-10, 12-15 are currently pending.

Applicant's information disclosure statement received June 20, 2005 is a duplicate of the information disclosure statement received Dec. 29, 2003, and it has not been considered. Please refer to applicant's copy of the 1449 marked "DUPLICATE" submitted herewith.

The previous claim objections set forth in paragraph 1 of the office action mailed Oct. 7, 2004 are withdrawn in view of applicant's amendment and the remarks contained therein.

The previous claim rejections under 35 USC 112, second paragraph, set forth in paragraph 2 of the office action mailed Oct. 7, 2004 are withdrawn in view of applicant's amendment and the remarks contained therein. However the rejection of claim 12 as being vague and indefinite stands for reasons given below in paragraph 2.

The previous claim rejections under 35 USC 102(b) and (a), set forth in paragraphs 3-4 of the office action mailed Oct. 7, 2004 are withdrawn in view of applicant's amendment and the remarks contained therein.

Finally, the previous claim rejection under 35 USC 103(a) set forth in paragraph 5 of the office action mailed Oct. 7, 2004 is withdrawn in view of applicant's amendment and the remarks contained therein.

However, applicant's amendment necessitates the following new ground(s) of rejection.

New Ground(s) of Rejection

Claim Rejection(s)—35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

1. Claims 1, 2, 4, 6-10, 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a limited number of cancer types, does not reasonably provide enablement for all cancers and solid tumors in general. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The claims are drawn to methods for treating cancer by administering an effective amount of a combination of a panerb B inhibitor and at least one antineoplastic agent.

(2) The state of the prior art

With respect to cancer, this a broad term which encompasses numerous forms of neoplastic diseases, each involving different types of tissues and organs and also includes blood borne diseases. As recognized in the art, many different anti-neoplastic drugs are used to treat a variety of cancers, but there is no one drug or one drug combination, which is capable of treating all cancers in general. Please see pages 1226-1229 of Goodman & Gilman's.

Additionally, Rao et al., disclose that CI-1033 potently inhibited the growth of ErbB-overexpressing breast cancer cells. Refer to paragraph 3 below.

WO '140 discloses a method for treating cancer disorders over-expressing ErbB2 by administering an anti-ErbB2 antibody in combination with a chemotherapeutic agent such as gemcitabine. The cancers that can be treated are lung cancer, pancreatic cancer, bladder cancer, etc. Refer to paragraph 3 below.

Finally, WO '828 discloses a method of treating cancers characterized by over-activity and/or inappropriate activity of erbB-2 (prostate, breast, pancreatic, colon, etc.), comprising administering to a patient in need thereof an effective amount of an erbB-2 inhibitor in combination with another anti-cancer compound (cisplatin) or radiation. Refer to paragraph 3 below.

(3) The relative skill of those in the art

The relative skill of those in the art is high. However, given the state of the art as set forth above, the artisan is currently unaware of any one particular combination of drugs that is effective in treating all cancer types.

(4) The predictability or unpredictability of the art

The unpredictability of the pharmaceutical and cancer art is high. Additionally, the lack

of significant guidance from the present specification or prior art with regard to the treatment of all cancers in a mammal, including a human, with the claimed compounds as the active ingredients makes practicing the claimed method unpredictable.

(5) The breadth of the claims

The claims are broad since they are drawn to the treatment of all cancer types.

(6) The amount of direction or guidance presented

The specification describes the use of synergistic combinations of an erb B inhibitor, more specifically, a panerb B inhibitor, and at least one other chemotherapeutic agent in the treatment of cancer in a mammal. However, Applicant's specification does not enable one of ordinary skill in the art to use the claimed invention in the treatment of the numerous neoplastic diseases covered by the term "cancer." Applicant's specification sets forth a limited number of cancer cell types, which would be treated by the claimed combination(s). The specification does not provide guidance as to how one of ordinary skill in the art would accomplish the objective of treating all types of cancer in a patient by administering the claimed combination(s).

(7) The presence or absence of working examples

Example 1 investigates the effect of a combination of CI-1033 (a panerb B inhibitor) and gemcitabine against implanted human pancreatic carcinoma in nude mice (page 15). Example 2 (page 17) provides data for the effectiveness of the combination of CI-1033 and paclitaxel against implanted human bladder carcinoma in nude mice. Other experiments are described using human breast carcinoma cells (in vitro) and in vivo tests using human epidermoid carcinoma (pages 20-21). Finally, examples 4-8 evaluate the effectiveness of combinations of CI-1033 and either docetaxel, etoposide, capecitabine, cisplatin or topotecan against implanted

human non small cell lung cancer cells, implanted murine colon carcinoma cells and human cell lung carcinoma cells. Please refer to pages 23-26.

(8) The quantity of experimentation necessary

In the absence of any sound evidence or scientific reasoning as to how the skilled artisan would extrapolate any results from the limited examples in the present disclosure as being reasonably suggestive of treating cancer (in general), the present disclosure is not determined to be enabling for the treatment of all types of cancers.

Additionally, in light of the state of the art (see **(2)** above), which conspicuously lacks recognition that all forms of cancer are treatable by the administration of one drug or one combination of drugs, and in view of the unpredictability of effectively treating cancer, it is highly unlikely, and the Office would require experimental evidence to support the contention, that the claimed combination of compound(s) could actually treat all cancers by simply administering, by any method, an amount of the claimed compounds.

Given what is presently claimed, what is presently disclosed, and given what is supported by adequate description in the specification, one of ordinary skill in the art would have no alternative recourse ***but*** undue experimentation in order to determine how the present invention could be used to treat all forms of cancer including all types of solid tumors as well as blood-borne tumors.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-15 recite the limitation "the panerb B tyrosine kinase inhibitor" in line 2. There is insufficient antecedent basis for this limitation in the claim.

Claim 12 remains vague and indefinite because in line 3, the limitation "taxotere" lacks sufficient antecedent basis. Please refer to page 3 of the office action mailed Oct. 7, 2004.

Claim Rejection(s)—35 USC 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

3. Claims 1, 2, 4, 6-10, 12-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 9931140 ('140) and WO 0241828 ('828) in view of Rao et al. (all references already of record).

WO '140 discloses a method for treating cancer disorders over-expressing ErbB2 (e.g. breast, pancreatic, etc.), the method comprising administering to a patient in need thereof an effective amount of an anti-ErbB2 antibody in combination with a chemotherapeutic agent such as gemcitabine. The chemotherapeutic agent is preferably is a taxoid such as paclitaxel. The cancers that can be treated are lung cancer, pancreatic cancer, bladder cancer, etc. Finally, WO '140 teaches that the two agents can be administered at the same time or consecutively, in either order. Please see the abstract; page 3, page 10, lines 10-35; page 11; page 25, lines 34-38.

WO '828 discloses a method of treating cancers characterized by over-activity and/or inappropriate activity of erbB-2 (prostate, breast, pancreatic, colon, etc.), the method comprising administering to a patient in need thereof an effective amount of an erbB-2 inhibitor selected from the group consisting of soluble extract of houttuyninum, or compound houttuyninum, Houttuynia cordata, neo-houttuyninum or analogs thereof. WO '828 also discloses that the erbB-2 inhibitors may be administered in combination with another anti-cancer compound (cisplatin) or radiation. Please see the abstract; page 13, line 1; claims 1-15.

WO '140 and WO '828 do not disclose treating the specific cancers by administering a panerb B inhibitor such as N-[4-(3-chloro-4-fluoro-phenylamino)-7-(3-morpholin-4-yl-propoxy)-

quinazolin-6-yl]-acrylamide (also known as CI-1033; see claim 4). However, the examiner refers to Rao et al., which teach that CI-1033 potently inhibited the growth of ErbB-overexpressing breast cancer cells. In fact, a three times weekly administration schedule resulted in sustained growth inhibition, and modest cytotoxicity was observed. Please see the abstract, page 1519; RESULTS, pages 1521-1522; Figures 2(a)-2(b).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the treatment methods of WO '140 and WO '828 by substituting the erbB tyrosine kinase inhibitors taught by WO '140 and '828 with the panerbB tyrosine kinase inhibitor CI-1033 because, in view of the potent inhibitory properties observed by Rao et al., one of ordinary skill in the art would reasonably expect CI-1033 to significantly inhibit the growth or proliferation of erbB-overexpressing breast cancer cells in a patient in need thereof. Moreover, absent evidence to the contrary, one of ordinary skill in the art would reasonably expect the erbB inhibitor CI-1033 to inhibit the growth or proliferation of other cancer cell types disclosed by WO '140 and '828 which overexpress erbB family of growth factor receptors. Finally, since both WO '140 and '828 suggest the treatment of the disclosed cancers would be more effective with administration of an additional chemotherapeutic agent, it would have been obvious and reasonable to conclude that the additive effect of the combination of CI-1033 and the chemotherapeutic agent would successfully treat the patient suffering from breast cancer or other specific cancer with inappropriate activity of erbB-2.

Conclusion

Claims 1, 2, 4, 6-10, 12-15 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Cybille Delacroix-Muirheid** whose telephone number is **571-272-0572**. The examiner can normally be reached on Mon-Thurs. from 8:30 to 6:00 as well as every other Friday from 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Christopher Low**, can be reached on **571-272-0951**. The fax phone number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CDM
Feb. 1, 2006

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